Food, Medicine and Healthcare Administration and Control Authority of Ethiopia (FMHACA)

Guidelines for Registration of Similar Biotherapeutic Products (SBPs)

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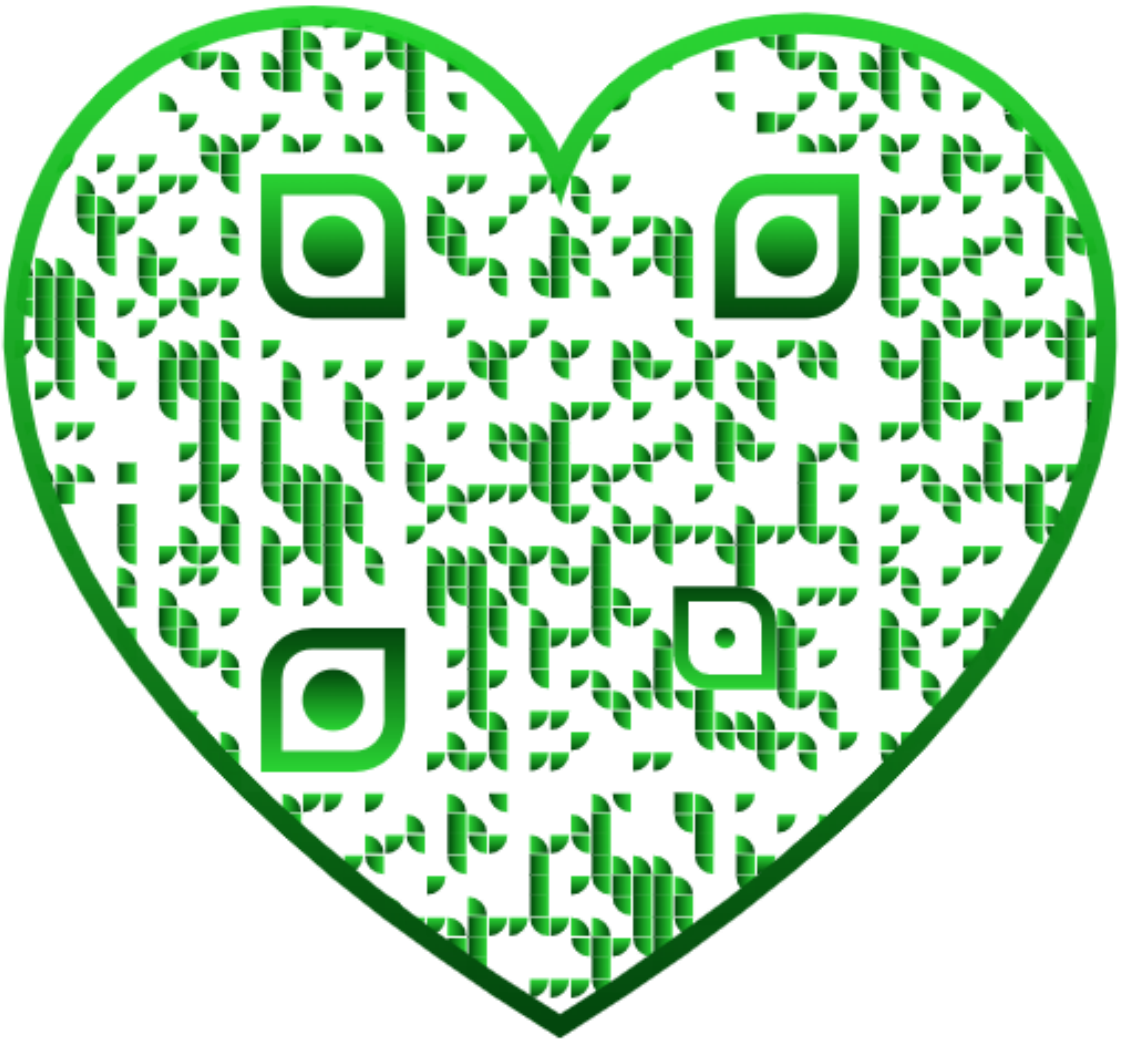
Addis Ababa, Ethiopia



This guideline is adapted from Guidelines on evaluation of similar biotherapeutic products (SBPs), Annex 2, WHO Technical Report Series No. 977, WHO Expert Committee on Biological Standardization Sixtieth Report, Geneva, 2013. It is a basis for establishing regulatory frameworks for licensing of SBPs.

Table of Contents

ACKNOWLEDGEMENT v

FORWARD vi

1. Introduction 1

2. Scope 2

3. Objective 2

4. Glossary 3

5. ADMINSTRATIVE AND PRODUCT INFORMATION 5

5.1. Covering Letter 5

5.2. Table Contents of the dossier 5

5.3. Application Form 5

5.4. Agency Agreement 5

5.5. Good Manufacturing Practice and Certificate of Pharmaceutical Product 6

5.6. Regulatory situation in other countries 6

5.7. Product information 7

5.7.1. Summary of Product Characteristics 7

5.7.2. Labeling (immediate and outer label) 7

5.7.3. Patient Information Leaflet (PIL) or Package Insert 8

5.7.4. Evidence for an application fee 8

6. Scientific considerations and concept for licensing SBPs 8

6.1. Comparability exercise 10

7. Key principles for the licensing of SBPs 10

8. Reference biotherapeutic products (RBPs) 12

8.1. Considerations for choice of RBP 12

9. Quality 13

9.1. Manufacturing process 15

9.2. Characterization 16
9.2.1. Physicochemical Properties 17
9.2.2. Biological Activity 17
9.2.3. Immunochemical properties 19
9.2.4. Impurities 19
9.3. Specifications 19
9.4. Analytical techniques 20
9.5. Stability 21
10. Nonclinical evaluation 21
10.1. General considerations 22
10.2. Special Considerations 22
10.2.1. In vitro studies 23
10.2.2. In vivo studies 23
11. Clinical evaluation 25
11.1. Pharmacokinetic studies 25
11.2. Pharmacodynamic studies 28
11.3. Confirmatory pharmacokinetic/pharmacodynamic studies 28
11.4. Efficacy studies 29
11.4.1. Advantages and disadvantages of equivalence/ non-inferiority designs for SBPs 31
11.4.2. Statistical considerations for the design and analysis of equivalence/non-inferiority trials for SBPs 31
11.5. Safety 34
11.6. Immunogenicity 35
11.7. Extrapolation of efficacy and safety data to other clinical indications 37
12. Pharmacovigilance 38
13. Prescribing information and label 39

ANNEXES 40

ANNEX I: Application form for registration 40

ANNEX II: Certificate of pharmaceutical products[1] 46

ANNEX III: Summary of product characteristics 51

ANNEX IV: Requirements for Registration of Products Accepted by Stringent Regulatory Authority 55

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The Authority would also like to acknowledge its staff and all experts who provide their heling hands for the invaluable contributions in the development of this document.

FORWARD

Ethiopia has been made huge strides to improve access to safe, quality and efficacious medicines to the public. The Ethiopian Food, Medicine and Healthcare Administration and Control Authority is responsible to ensure the safety, quality and effectiveness of similar biotherapeutic products (SBPs). Similar biotherapeutic products are pharmaceutical products that fall in this jurisdiction and must be regulated as stipulated in the proclamation No. 661/2009.

Similar biotherapeutic products are biotherapeutics that are similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product. These products rely for their licensing partly on prior information regarding safety and efficacy obtained with the originator products. The clinical experience and established safety profile of the originator products contribute to the development of SBPs. The approach established for generic medicines is not suitable for the development, evaluation and licensing of SBPs since biotherapeutics consist of relatively large and complex proteins that are difficult to characterize. The clinical performance of biotherapeutics can also be much influenced by the manufacturing process and some clinical studies will also be required to support the safety and efficacy of SBPs. This requires establishing special regulatory requirements for registration of SBPs that addresses its unique nature.

The authority is striving to establish robust system that strengthen the evaluation process for quality, safety and efficacy of SBPs for human use and ensuring compliance for Good Manufacturing Practices (GMP). In this guideline, the authority has set the required procedures and requirements for SBPS dossier assessment. I believe that successful implementation of this guideline will help us to achieve access to safe, quality and effective SBPs to the community. Hence, I call up on health professionals, pharmaceutical organizations, development partners and all stakeholders to put a coordinated effort to realize this guideline.

I have no doubt that with the commitment and engagement of the applicants for market authorization to comply with the regulatory requirements and the support of our development partners, we will prevail to implement the aforementioned guideline.

Finally, I would like to take this opportunity to acknowledge and express my appreciation to the United States Agency for International Development (USAID) and the U. S. Pharmacopeial

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1. INTRODUCTION

The Ethiopian Food, Medicine and Healthcare Administration and Control Authority is mandated by the proclamation Nº. 661/2009 to ensure the safety, quality and efficacy of medicines. Biotherapeutics are pharmaceutical products that fall in this jurisdiction that must be available in the market of Ethiopia of required safety, quality and effectiveness.

Biotherapeutics are products of biological origin that exhibit some intrinsic variability. They are characterized by complex manufacturing processes. The quality of biotherapeutics cannot be assessed solely by testing the final product alone. Hence, Specific regulatory systems for these products should also be strengthened.

Biotherapeutic products (biotherapeutics) have a successful record in treating many life-threatening and chronic diseases. However, their cost has often been high, thereby limiting their accessibility to patients, particularly in developing countries. Recently, the expiry of patents and/or data protection for the first major group of originator's biotherapeutics has ushered in an era of products that are designed to be "similar" to a licensed originator product. These products rely for their licensing partly on prior information regarding safety and efficacy obtained with the originator products. The clinical experience and established safety profile of the originator products should contribute to the development of similar biotherapeutic products (SBPs). A variety of terms, such as "biosimilar products", "follow-on protein products" and "subsequent-entry biologics" have been coined to describe these products.

The term "generic" medicine is used to describe chemical, small molecule medicinal products that are structurally and therapeutically equivalent to an originator product whose patent and/or data protection period has expired. Demonstration of bioequivalence of the generic medicine to a reference product is usually appropriate and sufficient proof of therapeutic equivalence between the two. However, the approach established for generic medicines is not suitable for the development, evaluation and licensing of SBPs since biotherapeutics consist of relatively large and complex proteins that are difficult to characterize. The clinical performance of biotherapeutics can also be much influenced by the manufacturing process and some clinical studies will also be required to support the safety and efficacy of a SBP.

This document is intended to provide guidance for the development and evaluation of SBPs; it should be viewed as a "living" document that will be developed further in line with advances in

scientific knowledge and experience. It is essential that the standard of evidence supporting the decisions to license SBPs be sufficient to ensure that products meet acceptable levels of quality, safety and efficacy for public health purposes. Elaboration of the data requirements and considerations for the licensing of these products is expected to facilitate development of and worldwide access to biotherapeutics of assured quality, safety and efficacy at more affordable prices. In most cases, their authorization will be evaluated on a case-by-case basis, and the amount of data required by the Authority may vary.

It is important to note that biotherapeutics that are not shown to be similar to a reference biotherapeutic product (RBP) as indicated in these Guidelines should neither be described as "similar" nor called SBPs. Such products could be licensed through the usual processes, using more extensive nonclinical and clinical data sets or full licensing applications.

All users of this guideline are strongly invited to forward their comments and suggestions to the Food, Medicine and Healthcare Administration and Control Authority of Ethiopia, P.O. Box 5681, Tel. 251-11 552 41 22, email: regulatory@fmhaca.gov.et, Addis Ababa, Ethiopia.

2. SCOPE

This Guideline applies to well-established and well-characterized biotherapeutic products such as recombinant DNA-derived therapeutic proteins. Vaccines and plasma-derived products and their recombinant analogues are excluded from the scope of this document.

For guidance specific to post-market changes, applicant may refer the Guidelines for Submission of Post-Approval Variation Medicine Applications, 2015. For guidance specific to re-registration applications, applicant may refer the Guidelines for Registration of Medicine, 2014, Appendix 4

3. OBJECTIVE

The intention of this document is to provide acceptable principles for licensing of biotherapeutic products that are claimed to be similar to biotherapeutic products of assured quality, safety and efficacy that have been licensed based on a full licensing dossier. On the basis of proven similarity, the licensing of a SBP will rely, in part, on nonclinical and clinical data generated with an already licensed RBP.

4. GLOSSARY

The definitions given below apply to the terms used in this Guideline. They may have different meanings in other contexts.

Comparability exercise: Head-to-head comparison of a biotherapeutic product with a licensed originator product with the goal of establishing similarity in quality, safety and efficacy. Products should be compared in the same study using the same procedures.

Drug product: A pharmaceutical product type that contains a drug substance, generally in association with excipients.

Drug substance: The active pharmaceutical ingredient and associated molecules that may be subsequently formulated, with excipients, to produce the drug product. It may be composed of the desired product, product-related substances, and product- and process-related impurities. It may also contain other components such as buffers.

Equivalent: Equal or virtually identical in the parameter of interest. Equivalent efficacy of two medicinal products means they have similar (no better and no worse) efficacy and any observed differences are of no clinical relevance.

Generic medicine: A generic medicine contains the same active pharmaceutical ingredient as, and is bioequivalent to, an originator (comparator) medicine. Since generic medicines are identical in the active pharmaceutical substance, dose, strength, route of administration, safety, efficacy and intended use, they can be substituted for the originator product.

Head-to-head comparison: Direct comparison of the properties of the SBP with the RBP in the same study.

Immunogenicity: The ability of a substance to trigger an immune response or reaction (e.g. development of specific antibodies, T cell response, allergic or anaphylactic reaction).

Impurity: Any component present in the drug substance or drug product that is not the desired product, a product-related substance, or excipient including buffer components. It may be either process- or product-related.

Non-inferior: Not clinically inferior to a comparator in the parameter studied. A non-inferiority clinical trial is one that has the primary objective of showing that the response to the investigational product is not clinically inferior to a comparator by a pre-specified margin.

Originator product: A medicine that has been licensed by the national regulatory authorities on the basis of a full registration dossier; i.e. the approved indication(s) for use were granted on the basis of full quality, efficacy and safety data.

Pharmacovigilance: The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.

Reference biotherapeutic product (RBP): A reference biotherapeutic product is used as the comparator for head-to-head comparability studies with the similar biotherapeutic product in order to show similarity in terms of quality, safety and efficacy. Only an originator product that was licensed on the basis of a full registration dossier can serve as an RBP. The term does not refer to measurement standards such as international, pharmacopoeial or national standards or reference standards.

Similarity: Absence of a relevant difference in the parameter of interest.

Similar biotherapeutic product (SBP): A biotherapeutic product that is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.

Well-established biotherapeutic product: A biotherapeutic product that has been marketed for a suitable period of time with a proven quality, efficacy and safety.

5. ADMINSTRATIVE AND PRODUCT INFORMATION

5.1. COVERING LETTER

Dated and signed letter for submission of the dossier by mentioning the product included in the dossier from the manufacturer responsible for registration. The letter should declare that the information provided in the dossier is true and correct.

5.2. TABLE CONTENTS OF THE DOSSIER

Table of contents should be provided.

5.3. APPLICATION FORM

Completed and signed application form as provided in Annex I of this Guideline should be submitted. The date of application should correspond to the date of submission of the registration dossier to the Authority.

5.4. AGENCY AGREEMENT

i. An agency agreement should be made between the manufacturer of the product for registration and the agent responsible for the import, distribution, and sale of the product in Ethiopia. Where the company manufactures the product at two or more places, the agreement and responsibility of each party made between the manufacturers should be submitted. In such a case, the agency agreement between the local agent and the manufacturer should be the site where the file is kept and the applicant for registration is registered.

ii. The agreement should be signed by both parties and such is what is to be presented. The seal/stamp of both parties should also be affixed to the document for agency agreement.

iii. The agreement should specify the first agent to handle the medicine registration process. In case the manufacturer wishes to have more than one distributor, this has to be mentioned in the agreement, but the maximum numbers of distributors are limited to three. The appointed agent(s) is responsible for correspondence and complete compliance with regulatory requirements pertaining to the product distribution life cycle in the country.

iv. The agreement should state that if any fraud or unsuspected and unacceptable adverse

event occurs to the consumer under normal utilization, all the party's (local agents, manufacturer, and/or license holder) mentioned in the agreement will be responsible for collecting the product from the market and will be responsible for substantiating any related consequences.

v. The agreement should specify that both parties are responsible for pharmacovigilance and post-marketing reporting of the product safety, quality, and efficacy follow-up after marketing.

vi. For the purpose of administration, the agreement should remain valid for the period of one year from the date of submission to the Authority unless it is found to be satisfactory for the termination of the agreement.

vii. The agent representing the manufacturer for importation should hold a license issued by the Ministry of Trade and a certificate of competence issued by the Authority at the time of importation of the product.

viii. In case the actual manufacturer has scientific office in Ethiopia, the agency agreement should indicate that the scientific office may be responsible for registration of medicines and the local agents are responsible for import and distribution.

5.5. GOOD MANUFACTURING PRACTICE AND CERTIFICATE OF PHARMACEUTICAL PRODUCT

A valid Good Manufacturing Practice (GMP) Certificate and market authorization certificate should be provided. Certificate of pharmaceutical product as a requirement for registration could be optional provided that valid cGMP Certificate or Market Authorization Certificate is submitted. The format of the CPP is provided in Annex II of this Guideline. The CPP should be valid. The CPP for the products should be in line with the explanatory notes of the CPP as provided in Annex III of this guideline.

5.6. REGULATORY SITUATION IN OTHER COUNTRIES

The countries should be listed in which this product has been granted a marketing authorization, this product has been withdrawn from the market and/or this application for marketing has been rejected, deferred, or withdrawn.

5.7. PRODUCT INFORMATION

Product information including package insert, labeling, and summary of product characteristics (SmPC) should be provided. All product information label statements are required to be in English. Any information appearing in the product information (labels, PIL, and SmPC) should be based on scientific justification.

5.7.1. SUMMARY OF PRODUCT CHARACTERISTICS

Recommended format for the content of the SmPC is provided in Annex III of this Guideline.

5.7.2. LABELING (IMMEDIATE AND OUTER LABEL)

Only original labels or computer-ready color-printed labels are accepted for final approval. In the case where the text of the labels is printed directly on plastic bottles through a silk screen process, photocopies of these labels will be accepted for approval.

The titles for batch number, manufacturing, and expiry dates should be part of the printing (typewritten materials, stickers, etc., are not acceptable). If the labeling technology of the manufacturer is such that this information is to be printed on the label during production, a written commitment to show all the required information on the label of the finished product must be submitted. The contents of the label should at least contain:

a) The name of the product– brand and generic/International Non-proprietary Name (INN);
b) Pharmaceutical form and route of administration;
c) Qualitative and quantitative composition of active ingredient(s), preservative(s), and antioxidant (s);
d) The volume of the contents, and/or the number of doses, or quantity in container;
e) Directions to consult the package insert or the carton label for complete directions for use;
f) Handling and storage conditions;
g) License number of the manufacturer;
h) Batch number;
i) Manufacturing date;
j) Expiry date; and,
k) Name and address of manufacturer.

5.7.3. PATIENT INFORMATION LEAFLET (PIL) OR PACKAGE INSERT

The general content of the PIL should be prepared in line with the content of the SmPC. The PIL should not be described or presented in a manner that is false, misleading, or deceptive or is likely to create an erroneous impression regarding its use in any respect, either pictorially or in words.

5.7.4. EVIDENCE FOR AN APPLICATION FEE

Each application should be accompanied by a relevant service fee for registration. Applicants are advised to contact the Authority for the amount and details of mode of payment.

6. SCIENTIFIC CONSIDERATIONS AND CONCEPT FOR LICENSING SBPs

Demonstration of structural sameness and bioequivalence of the generic medicine to the reference product is usually sufficient for therapeutic equivalence between the generic and reference product to be inferred. However, the generic approach is not suitable for the licensing of SBPs since biotherapeutic products usually consist of relatively large and complex entities that are difficult to characterize. In addition, SBPs are manufactured and controlled by processes established by the SBP manufacturer since the manufacturer of an SBP normally does not have access to all the necessary manufacturing information on the originator product. However, minor differences in the manufacturing process may affect the pharmacokinetics, pharmacodynamics, efficacy and/or safety of biotherapeutic products. It has consequently been agreed that the normal method for licensing generic medicines through bioequivalence studies alone is not scientifically appropriate for SBPs.

Decision-making regarding the licensing of SBPs should be based on scientific evidence. The onus is on the manufacturer of an SBP to provide the necessary evidence to support all aspects of an application for licensing. As in any drug development programme, development of an SBP is a stepwise approach that starts with characterization and evaluation of quality attributes of the product and is followed by nonclinical and clinical studies. Comprehensive characterization and comparison showing similarity at the quality level are the basis for possible data reduction in the nonclinical and clinical development. If differences between the SBP and the RBP are found at any step, the underlying reasons for the differences should be investigated. Differences should

always be fully explained and justified and may lead to additional data (e.g. on safety) being required.

In addition to quality data, nonclinical and clinical data are required for any SBP, generated with the product itself. The amount of such data that is considered necessary will depend on the product or class of products, on the extent of characterization possible using state-of-the-art analytical methods, on observed or potential differences between the SBP and the RBP, and on clinical experience with the product class (e.g. safety/immunogenicity concerns in a specific indication). A case-by-case approach is clearly needed for each class of products.

An SBP is intended to be similar to a licensed biotherapeutic product for which substantial evidence exists of safety and efficacy. Authorization of the SBP on the basis of reduced nonclinical and clinical data depends on proof of its similarity to an appropriate RBP through the comparability exercise. Manufacturers should demonstrate both a full understanding of their product and consistent and robust manufacture, and should submit a full quality dossier that includes a complete characterization of the product. Comparison of the SBP and the RBP with respect to quality represents an additional element to the "traditional" full quality dossier. A reduction in data requirements is therefore possible only for the nonclinical and/or clinical parts of the development programme. The dosage form and route of administration of the SBP should be the same as for the RBP.

Studies must be comparative in nature and must employ analytical methods that are capable of detecting potential differences between the SBP and the RBP. The main clinical studies should use the final formulation of the SBP, i.e. derived from the final process material, otherwise, additional evidence will be required to demonstrate that the SBP to be marketed is comparable to that used in the main clinical studies.

If similarity between the SBP and the RBP has been convincingly demonstrated, and if the manufacturer can provide scientific justification for such extrapolation, the SBP may be approved for use in other clinical indications for which the RBP is used but which have not directly been tested in clinical trials (see section 11.7). Any significant differences between the SBP and the chosen RBP detected during the comparability exercise would indicate that the products are not similar and that more extensive nonclinical and clinical data may be required to support the application for licensing.

6.1. COMPARABILITY EXERCISE

The comparability exercise is designed to show that the SBP has quality attributes that are highly similar to those of the RBP. To provide an integrated and comprehensive set of comparative data, however, it must also include the nonclinical and clinical studies. At the level of quality, the comparability data can be considered as additional data, over and above what is normally required for an originator product developed as a new and independent product; this is the basis for reducing the requirements for nonclinical and clinical data.

It is important that a distinction be made between the usual quality data requirements and those presented as part of the comparability exercises. It may be useful to present these as a separate section in the quality module.

7. KEY PRINCIPLES FOR THE LICENSING OF SBPS

- The development of an SBP involves stepwise comparability exercise(s) starting with comparison of the quality characteristics of the SBP and the RBP. Demonstration of similarity of an SBP to an RBP in terms of quality is a prerequisite for reducing the nonclinical and clinical data set required for licensure. After each step of the comparability exercise, the decision to proceed further with the development of the SBP should be evaluated.
- The licensing of a product as an SBP depends on its demonstrated similarity to a suitable RBP in quality, nonclinical and clinical parameters. The decision to license the product should be based on evaluation of the whole data package for each of these parameters.
- If relevant differences between the SBP and the RBP are found in the quality, nonclinical or clinical studies, the product is unlikely to qualify as an SBP, and a more extensive nonclinical and clinical data set will probably be required to support its application for licensure. Such a product should not qualify as an SBP as defined in this guideline.
- If comparability exercises and/or studies with the RBP are not performed throughout the development process as outlined in this document, the final product should not be referred to as an SBP.
- SBPs are not “generic medicines” and many characteristics associated with the authorization process generally do not apply.

- Like other biotherapeutic products, SBPs require effective regulatory oversight for the management of the potential risks they pose and in order to maximize their benefits.

8. REFERENCE BIOTHERAPEUTIC PRODUCTS (RBPs)

Applicant should provide sufficient information and appropriate rationale for selection of the RBPs. Comprehensive information on the RBP provides the basis for establishing the safety, quality and effectiveness profile to which the SBP is compared. The RBP also provides the basis for dose selection and route of administration, and is used in the comparability studies required to support the licensing application. The demonstration of an acceptable level of similarity between the SBP and RBP provides the rationale for a reduced nonclinical and clinical data set to support the application for market authorization for the SBP. The RBP is thus central to the licensing of an SBP.

To support licensure of the SBP, similarity of the SBP to the RBP should be demonstrated through head-to-head comparisons with the RBP. The same RBP should be used throughout the entire comparability exercise.

The choice of an RBP is critically important for the evaluation of the SBP. The rationale for the choice of RBP should be provided by the manufacturer of the SBP in the submission application for registration.

Principally, the Authority requires the use of nationally licensed originator product as RBP for comparability exercise. When there is no nationally licensed RBPs, the Authority may consider RBP licensed or resourced in other countries with proven efficacy and safety. Additionally the consideration of market experience, duration and volume of marketed use will be considered.

8.1. CONSIDERATIONS FOR CHOICE OF RBP

Since the choice of RBP is essential to the development of an SBP, the following should be considered.

- The RBP should have been marketed for a suitable duration and have a volume of marketed use such that the demonstration of similarity to it brings into relevance a substantial body of acceptable data regarding the safety and efficacy.
- The manufacturer must demonstrate that the chosen RBP is suitable to support the application for marketing authorization of an SBP.
- The RBP should have been licensed on the basis of full quality, safety, and efficacy data. An SBP should therefore not be chosen as an RBP.

- The same RBP should be used throughout the development of the SBP (i.e. throughout the comparative quality, nonclinical, and clinical studies).
- The drug substance of the RBP and the SBP must be shown to be similar.
- The dosage form and route of administration of the SBP should be the same as that of the RBP.
- The following factors should be considered in the choice of an RBP that is marketed in another jurisdiction.
    - ✓ The RBP should be licensed and widely marketed in another jurisdiction that has a well-established regulatory framework and principles, as well as considerable experience of evaluation of biotherapeutic products and post-marketing surveillance activities.
    - ✓ The acceptance of an RBP for evaluation of an SBP in a particular country does not imply that the NRA of that country has approved the RBP for use.

9. QUALITY

The quality comparison showing molecular similarity between the SBP and the RBP provides the essential rationale for predicting that the clinical safety and efficacy profile of the RBP should also apply to the SBP, meaning that the extent of the nonclinical and clinical data required for the SBP can be reduced. Ideally, development of an SBP involves thorough characterization of a number of representative lots of the RBP and then engineering a manufacturing process that will yield a product highly similar to the RBP in all clinically relevant quality attributes, i.e. product attributes that may impact clinical performance. An SBP is generally derived from a separate and independent master cell bank using independent manufacturing processes and control. These should be selected and designed to meet the required comparability criteria. A full quality dossier for both drug substance and drug product is always required and must comply with the standards required by authority for originator products.

Increased knowledge of the relationship between biochemical, physicochemical and biological properties of the product and clinical outcomes will facilitate development of an SBP. Because of the heterogeneous nature of proteins (especially those with extensive post-translational modifications, such as glycoproteins), the limitations of some analytical techniques, and the generally unpredictable nature of the clinical consequences of minor differences in protein

structural/physicochemical properties, the evaluation of comparability will have to be carried out independently for each product. For example, oxidation of certain methionine residues in one protein may have no impact on clinical activity whereas in another protein it may significantly reduce the intrinsic biological activity or increase immunogenicity. Thus, differences in the levels of methionine oxidation in the RBP and SBP would need to be evaluated and, if present, their clinical relevance would be evaluated and discussed.

To evaluate comparability, the manufacturer should carry out a comprehensive physicochemical and biological characterization of the SBP in head-to-head comparisons with the RBP. All aspects of product quality and heterogeneity should be assessed (see section 9.2).

A high degree of similarity between the SBP and the RBP is the basis for reducing the nonclinical and clinical requirements for licensing. However, some differences are likely to be found, for example as a result of differences in impurities or excipients. Such differences should be assessed for their potential impact on clinical safety and efficacy of the SBP and justification (for example, own study results or published data) for allowing such differences should be provided. Differences of unknown clinical relevance, particularly regarding safety, may have to be addressed in additional studies pre- or post-marketing. Differences in quality attributes known to have potential impact on clinical activity will influence the decision on whether to name such a product as an SBP. For example, if differences are found in glycosylation patterns that alter the biodistribution of the product and thereby change the dosing scheme, this product cannot be considered an SBP. Other differences between the SBP and RBP may be acceptable and would not trigger the need for extra nonclinical and/ or clinical evaluation. For example, a therapeutic protein that has lower levels of protein aggregates would, in most cases, be predicted to have a better safety profile than the RBP and would not need added clinical evaluation. In the same way, if heterogeneity in the terminal amino acids of the RBP is known to exist (and is adequately documented) but does not affect the bioactivity, distribution or immunogenicity of the RBP or similar products in its class, there may be no need for added clinical safety or efficacy studies based upon this heterogeneity of the RPB and SBP.

Due to the unavailability of drug substance for the RBP, the SBP manufacturer will usually be using a commercial drug product for the comparability exercise. The commercial drug product will, by definition, be in the final dosage form, containing the drug substance(s) formulated with

excipients. It should be verified that these excipients do not interfere with analytical methods and thus have no impact on test results. If the drug substance in the RBP needs to be purified from a formulated reference drug product in order to be suitable for characterization, studies must be carried out to demonstrate that product heterogeneity and relevant attributes of the active moiety are not affected by the isolation process. The approach used for isolating the SBP and comparing it with the RBP should be justified and demonstrated, with data, to be appropriate for the intended purpose. Where possible, the product should be tested with and without manipulation.

9.1. MANUFACTURING PROCESS

Manufacture of an SBP should be based on a comprehensively designed production process, taking all relevant guidelines into account. The manufacturer must demonstrate the consistency and robustness of the manufacturing process by implementing good manufacturing practices, modern quality control and assurance procedures, in-process controls, and process validation. The manufacturing process should meet the same standards as required by the authority for originator products. It should be optimized to minimize differences between the SBP and RBP in order to (a) maximize the reduction in clinical testing requirements for the SBP based upon the clinical history of the RBP, and (b) minimize any predictable impact on the clinical safety and efficacy of the product. Some differences between the SBP and RBP are expected and may be acceptable, provided that appropriate justification of the lack of impact on clinical performance can be given.

It is understood that a manufacturer developing an SBP will not have access to confidential details of the RBP manufacturing process; thus, unless there is a contractual arrangement with the manufacturer of the RBP, the process will differ from the licensed process for the RBP. The manufacturing process for an SBP should employ state-of-the-art science and technology to achieve a high-quality product that is as similar as possible to the RBP. This will involve extensive evaluation of the RBP before the manufacturing process for the SBP is developed. The SBP manufacturer should assemble all available knowledge of the RBP regarding the type of host cell, the formulation and the container closure system used for marketing the RBP. If applicable, the SBP manufacturer should then determine the potential impact of changing any one of these elements on product quality, safety and efficacy based on available evidence from information in the public domain and experience with use of the RBP. The SBP manufacturer is

encouraged to apply this knowledge to the design of the manufacturing process. The rationale for accepting these differences needs to be justified by sound science and by clinical experience with either the SBP or the RBP.

As a general rule, the product should be expressed and produced in the same host cell type as the RBP (e.g. Escherichia coli, Chinese hamster ovary cells, etc.) in order to minimize the potential for important changes in critical quality attributes of the protein and to avoid introduction of certain types of process-related impurities (e.g. host cell proteins, endotoxins, or yeast mannans) that could affect clinical outcomes and immunogenicity. The host cell type for manufacture of the SBP should be changed only if the manufacturer can demonstrate convincingly that the structure of the molecule is not affected or that the clinical profile of the product will not change. For example, somatropin produced in yeast cells appears to have similar characteristics to somatropin expressed in E. coli. In most cases, however, the use of a different host cell type will not be feasible for glycoproteins because glycosylation patterns vary significantly between different host cell types.

A complete description and data package should be provided that delineates the manufacturing process, starting with development of expression vectors and cell banks, cell culture/fermentation, harvest, purification and modification reactions, filling into bulk or final containers, and storage. The development studies conducted to establish and validate the dosage form, formulation, container closure system (including integrity to prevent microbial contamination) and usage instructions should be also documented (see relevant guidelines, such as those issued by the International Council for Harmonization of Technical Requirements for pharmaceuticals for Human Use (ICH)).

9.2. CHARACTERIZATION

Thorough characterization of both RBP and SBP should be carried out using appropriate, state-of-the-art biochemical, biophysical and biological analytical techniques. For the active ingredient(s) (i.e. the desired product), details should be provided on primary and higher-order structure, post-translational modifications (including, but not limited to, glycoforms), biological activity, purity, impurities, product-related (active) substances (variants), and immunochemical properties, where relevant.

When conducting a comparability exercise, head-to-head characterization studies are required to compare the SBP and the RBP. The primary structure of the SBP and the RBP should be identical.

If differences between the SBP and the RBP are found, their potential impact on safety and efficacy of the SBP should be evaluated. The predefined limits need to be considered in advance. Assessment of the results should include investigation of the differences found between the SBP and the RBP. This determination will be based upon knowledge of the relationship between product quality attributes and clinical activity of the RBP and related products, the clinical history of the RBP, and lot-to-lot differences for commercial lots of the RBP. For example, quality attributes such as composition and profile of glycosylation, biological activity that is known to be related to clinical activity, and receptor binding activity should be justified.

Knowledge of the analytical limitations of each technique used to characterize the product (e.g. limits of sensitivity, resolving power) should be applied when determining similarity. Representative raw data should be provided for all complex analytical methods (e.g. high-quality reproductions of gel and chromatograms) in addition to tabular data summarizing the complete data set and showing the results of all release and characterization analyses carried out on the SBP and the RBP.

The criteria outlined in the following sections should be considered when conducting the comparability exercise.

9.2.1. Physicochemical Properties

The physicochemical characterization should include determination of primary and higher-order structure (secondary/tertiary/quaternary) using appropriate analytical methods (e.g. mass spectrometry or nuclear magnetic resonance) and other biophysical properties. An inherent degree of structural heterogeneity occurs in proteins as a result of the biosynthesis process, such that the RBP and the SBP are likely to contain a mixture of post-translationally modified forms. Appropriate efforts should be made to investigate, identify and quantify these forms.

9.2.2. Biological Activity

Biological activity is the specific ability or capacity of the product to achieve a defined biological effect. It serves multiple purposes in the assessment of product quality and is required

for characterization and for batch analysis. Ideally, the biological assay will reflect the understood mechanism of action of the protein and will thus serve as a link to clinical activity. A biological assay is a quality measure of the "function" of the protein product and can be used to determine whether a product variant has the appropriate level of activity (i.e. a product related substance) or is inactive (and is therefore defined as an impurity). The biological assay also complements the physicochemical analyses by confirming the correct higher-order structure of the molecule. Thus, the use of relevant biological assay(s) with appropriate precision and accuracy provides an important means of confirming that there is no significant functional difference between the SBP and the RBP.

For a product with multiple biological activities, manufacturers should perform, as part of product characterization, a set of relevant functional assays designed to evaluate the range of activities of the product. For example, certain proteins possess multiple functional domains that express enzymatic and receptor-binding activities. In such situations, manufacturers should evaluate and compare all relevant functional activities of the SBP and the RBP.

Potency is the quantitative measure of the biological activity. A relevant, validated potency assay should be part of the specification for a drug substance and/or drug product. The results of the potency assay should be provided and expressed in units of activity. Where possible (e.g. for in vitro biochemical assays, such as enzyme assays or binding assays), the results may be expressed as specific activities (e.g. units/mg protein). Assays should be calibrated against an international or national standard or reference reagent, when available and appropriate. WHO provides International Standards and Reference Reagents, which serve as reference sources of defined biological activity expressed in an international unit (IU) or unit (U). International Standards and Reference Reagents are intended for calibration of national reference standards (http://www.who.int/ biologicals/reference preparations/en/). International or national standards and Reference Reagents should therefore be used to determine the potency and to express results in IU or U. They are not intended for use as RBPs during the comparability exercise.

Biological assays can be used for purposes other than determination of potency. For example, a relevant biological assay is essential for determining whether antibodies that develop in response to the product have neutralizing activity that affects the biological activity of the product and/or endogenous counterparts, if present (see section 11.6).

9.2.3. Immunochemical properties

When immunochemical properties are part of the characterization (e.g. for antibodies or antibody-based products), the manufacturer should confirm that the SBP is comparable to the RBP in terms of specificity, affinity, binding kinetics, and fragment crystallisable (Fc) functional activity, where relevant.

9.2.4. Impurities

Because access to all necessary information on the manufacturing process as well as on the drug substance of the originator product is limited, it is recognized that evaluation of the similarity of the impurity profiles of the SBP and the RBP will be generally difficult. Nevertheless, process- and product-related impurities should be identified, quantified by state-of-the-art technology and compared between the SBP and RBP. Some differences may be expected because the proteins are produced by different manufacturing processes. If significant differences in the impurity profiles of the SBP and the RBP are observed, their potential impact on efficacy and safety, including immunogenicity, should be evaluated. It is critical to have suitable assays for process-related impurities, specific to the cell line used for production.

9.3. SPECIFICATIONS

Specifications are employed to verify the routine quality of the drug substance and drug product rather than to fully characterize them. Specifications for an SBP, as for any biotherapeutic product, should be set as described in established guidelines and monographs, where these exist. It should be noted that pharmacopoeial monographs may provide only a minimum set of requirements for a particular product, and additional test parameters may be required. Reference to analytical methods used and acceptance limits for each test parameter of the SBP should be provided and justified. All analytical methods referenced in the specification should be validated; the corresponding validation should be documented.

Specifications for an SBP will not be the same as for the RBP since the manufacturing processes will be different and different analytical procedures and laboratories will be used for the assays. Nonetheless, the specifications should capture and control important known product quality attributes for the RBP (e.g. correct identity; purity, potency; molecular heterogeneity in terms of size, charge, and hydrophobicity, if relevant; degree of sialylation; number of individual

polypeptide chains; glycosylation of a functional domain; aggregate levels; impurities such as host cell protein and DNA). The setting of specifications should be based upon the manufacturer's experience with the SBP (e.g. manufacturing history; assay capability; safety and efficacy profile of the product) and the experimental results obtained by testing and comparing the SBP and RBP. Sufficient lots of SBP should be employed in setting specifications. The manufacturer should demonstrate, whenever possible, that the limits set for a given specification are not significantly wider than the range of variability of the RBP over the shelf-life of the product, unless justified.

9.4. ANALYTICAL TECHNIQUES

Although the power of analytical methods for characterization of proteins has increased dramatically over the past few decades, there are still obstacles to complete characterization of complex biotherapeutic products. A battery of state-of-the-art analyses is needed to determine structure, function, purity and heterogeneity of the products. The methods used should separate and analyse different variants of the product based upon different underlying chemical, physical and biological properties of protein molecules. For example, polyacrylamide gel electrophoresis (PAGE), ion exchange chromatography, isoelectric focusing, and capillary electrophoresis all separate proteins based upon charge, but they do so under different conditions and on the basis of different physicochemical properties. As a result, one method may detect variants that another method does not. The goal of the comparability investigation is to be as comprehensive as possible in order to minimize the possibility of undetected differences between the RBP and the SBP that may affect clinical activity. The analytical limitations of each technique (e.g. limits of sensitivity or resolving power) should be considered when determining the similarity between an SBP and an RBP.

The measurement of quality attributes in characterization studies (as opposed to in the specifications) does not necessarily require the use of validated assays, but the assays should be scientifically sound and qualified; that is, they should provide results that are meaningful and reliable. The methods used to measure quality attributes for lot release should be validated in accordance with relevant guidelines, as appropriate. A complete description of the analytical techniques employed for release and characterization of the product should be provided in the dossier application.

9.5. STABILITY

The stability studies should comply with relevant guidance as recommended by the authority. Studies should be carried out to show which release and characterization methods are stability-indicating for the product. Generally, stability studies should be summarized in an appropriate format, such as tables, and they should include results from accelerated degradation studies and studies under various stress conditions (e.g. temperature, light, humidity and mechanical agitation).

Accelerated stability studies are an important element of the determination of similarity between an SBP and an RBP because they can reveal otherwise hidden properties of a product that warrant additional evaluation. They are also important for identifying the degradation pathways of a protein product. The results obtained from accelerated stability studies may show that additional controls should be used in the manufacturing process and during shipping and storage in order to ensure the integrity of the product. Head-to-head accelerated stability studies comparing the SBP with the RBP will be of value in determining the similarity of the products by showing a comparable degradation profile. Currently, however, stress testing carried out in a comparative manner does not provide an added value. Representative raw data showing the degradation profiles for the product should be provided in the dossier application.

The stability data should support the conclusions regarding the recommended storage and shipping conditions and the shelf-life/storage period for the drug substance, drug product, and process intermediates that may be stored for significant periods of time. Stability studies on drug substance should be carried out using containers and conditions that are representative of the actual storage containers and conditions. Stability studies on drug product should be carried out in the intended drug product container-closure system. Real-time/ real-temperature stability studies will determine the storage conditions and expiry dating for the product, which may or may not be the same as for the RBP.

10. NONCLINICAL EVALUATION

The nonclinical part of the Guidelines addresses the pharmacotoxicological assessment of the SBP. Establishing the safety and efficacy of an SBP usually requires the generation of some nonclinical data for the SBP.

10.1. GENERAL CONSIDERATIONS

Demonstrating a high degree of molecular similarity between the SBP and the RBP should significantly reduce the need for nonclinical studies, since the RBP will already have a significant clinical history. Unless otherwise justified, nonclinical studies should be conducted with the final formulation of the SBP intended for clinical use.

The design of an appropriate nonclinical study programme requires a clear understanding of the product characteristics. Results from the physicochemical and biological characterization studies should be reviewed from the point of view of potential impact on efficacy and safety. In the development of an SBP, some existing guidelines (for example, ICH S6, Preclinical safety evaluation of biotechnology-derived pharmaceuticals) may be relevant and should therefore be taken into account. SBPs often require unique approaches to assessing their safety in nonclinical studies. Problems in the nonclinical evaluation of SBPs containing biotechnology-derived recombinant proteins as drug substance are often related to the fact that these products:

- may show species-specific pharmacodynamic activity such that it is sometimes difficult to identify a relevant species for pharmacodynamic and toxicological evaluation; and/or
- will, as “foreign proteins”, usually elicit an antibody response in long- term animal studies, and the formation of antibody complexes with the drug substance may make it difficult to interpret the results of subchronic or chronic repeat-dose studies.

10.2. SPECIAL CONSIDERATIONS

Nonclinical evaluation of a new biotherapeutic normally encompasses a broad spectrum of pharmacodynamic, pharmacokinetic and toxicological studies. The amount of additional nonclinical data required to establish the safety and efficacy of an SBP is considered to be highly dependent on the product and on factors related to substance class. Factors that often elicit the need for additional nonclinical studies include, but are not restricted to, the following:

- Quality-related factors:
  - significant differences in the cell expression system compared with the RBP;
  - significant differences in purification methods used;
  - the presence of a complex mixture of less well-characterized product- and/or process-related impurities.

- Factors related to pharmacotoxicological properties of the drug substance:
  - mechanism(s) of drug action are unknown or poorly understood;
  - the drug substance is associated with significant toxicity and/or has a narrow therapeutic index;
  - limited clinical experience with the RBP.

Depending on these factors, the spectrum of studies required to establish the safety and efficacy of the SBP may vary considerably and should be defined on a case-by-case basis. For example, in the case of a highly complex drug substance that is difficult to characterize by analytical techniques and that possesses a narrow therapeutic index, the nonclinical development programme may encompass a significant portion of the spectrum of studies described in relevant guidelines such as ICH S6. On the other hand, for products for which the drug substance and the impurity profile are well characterized by analytical means, which possess a wide therapeutic index and for which extensive clinical experience is available, the nonclinical development programme will probably be more limited. However, a head-to-head repeat-dose toxicity study should usually constitute a minimum requirement for nonclinical evaluation of an SBP. The nonclinical studies constitute a part of the overall comparability exercise. They should therefore be comparative in nature and designed to detect differences in response between the SBP and the RBP and not just the response to the SBP alone. Any deviation from this approach should be appropriately justified.

10.2.1. In vitro studies

Assays such as receptor-binding studies or cell-based assays (e.g. cell-proliferation or cytotoxicity assays) should normally be undertaken to establish comparability of the biological/pharmacodynamic activity of the SBP and the RBP. Such data are usually already available from the biological assays described in the quality part of the dossier (see section 9.2.2). Reference to these studies can be made in the nonclinical part of the dossier.

10.2.2. In vivo studies

Animal studies should be designed to maximize the information obtained. They should be comparative in nature (see above), should be performed in a species known to be relevant (i.e. a species in which the RBP has been shown to possess pharmacodynamic and/or toxicological

activity), and should employ state-of the-art technology. Where the model allows, consideration should be given to monitoring a number of end-points such as:

- Biological/pharmacodynamic activity relevant to the clinical application. These data should usually be available from biological assays described in the quality part of the dossier (see section 9.2.2) and reference to these studies can be made in the nonclinical part of the dossier. If feasible, biological activity may be evaluated as part of the nonclinical repeat-dose toxicity study (described below). In vivo evaluation of biological/pharmacodynamic activity may be unnecessary if in vitro assays are available that have been validated as reliably reflecting the clinically relevant pharmacodynamic activity of the RBP.
- Nonclinical toxicity as determined in at least one repeat-dose toxicity study carried out in a relevant species and including toxicokinetic measurements. Toxicokinetic measurements should include determination and characterization of antibody responses, including anti-product antibody titres, cross-reactivity with homologous endogenous proteins, and product-neutralizing capacity. The studies should be of sufficient duration to allow detection of potential differences in toxicity and antibody responses between the SBP and the RBP.

Besides being a part of the overall comparability exercise, the comparative repeat-dose toxicity study is considered to provide reassurance that no "unexpected" toxicity will occur during clinical use of the SBP. If performed with the final formulation intended for clinical use, the repeat-dose toxicity study will, in principle, allow for detection of potential toxicity associated both with the drug substance and with product- and process-related impurities.

Although the predictive value of animal models for immunogenicity in humans is considered low, antibody measurements, if applicable, should be included in the repeat-dose toxicity study to aid in the interpretation of the toxicokinetic data and in assessing, as part of the overall comparability exercise, whether important differences in structure or immunogenic impurities exist between the SBP and the RBP (the immunological response may be sensitive to differences not detected by laboratory analytical procedures).

Depending on the route of administration, local tolerance may need to be evaluated. If feasible, this evaluation may be performed as part of the described repeat-dose toxicity study.

On the basis of the demonstration of similarity between the SBP and RBP by the additional comparability exercise performed as part of the quality evaluation, other routine toxicological studies – such as safety pharmacology, reproductive toxicology, genotoxicity and carcinogenicity studies – are not generally requirements for the nonclinical testing of an SBP, unless triggered by results of the repeat-dose toxicity study or the local tolerance study and/or by other known toxicological properties of the RBP (e.g. known adverse effects of the RBP on reproductive function).

11. CLINICAL EVALUATION

The main/pivotal clinical data should be generated using the product derived from the final manufacturing process, which reflects the product for which marketing authorization is sought. Any deviation from this recommendation needs to be justified and additional data may be required, such as from pharmacokinetic bridging studies comparing the pharmacokinetic profiles of the products from the previous and final formulations. For changes in the manufacturing process, ICH Q5E should be followed.

Clinical studies should be designed to demonstrate comparable safety and efficacy of the SBP compared to RBP and therefore need to employ testing strategies that are sensitive enough to detect any relevant differences between the products.

The clinical comparability exercise is a stepwise procedure that should begin with pharmacokinetic and pharmacodynamic studies and continue with the pivotal clinical trials. If relevant differences between the SBP and the RBP are detected at any stage, the reasons need to be explored and justified. If this is not possible, the new product may not qualify as an SBP and a full licensing (standalone) application should be considered.

11.1. PHARMACOKINETIC STUDIES

The pharmacokinetic profile is an essential part of the basic description of a medicinal product and should always be investigated. Pharmacokinetic studies should generally be performed for the routes of administration applied for and using doses within the therapeutic dose range recommended for the RBP.

Pharmacokinetic studies must be comparative in nature and should be designed to enable the detection of potential differences between the SBP and the chosen RBP. This is usually best

achieved by performing single-dose, crossover pharmacokinetic studies in a homogenous study population and by using a dose at which the sensitivity to detect differences is greatest. For example, for a medicinal product with saturable absorption (saturation kinetics), the lowest therapeutic dose would be most appropriate, provided that the assay used can measure the resulting drug plasma levels with sufficient accuracy and precision.

To reduce any variability that is unrelated to differences between products, pharmacokinetic studies could be performed in healthy volunteers (if considered ethical and scientifically justified). If the drug substance under investigation is known to have adverse effects and the pharmacological effects or risks are considered unacceptable for healthy volunteers, it may be necessary to perform the pharmacokinetic studies in the proposed patient population.

In general, single-dose pharmacokinetic studies will suffice. However, in cases of dose-or time-dependent pharmacokinetics, resulting in markedly higher concentrations at steady-state than would be expected from single-dose data, a potential difference in the extent of absorption of the SBP and RBP may be greater at steady state than after single-dose administration. In such cases, it may be advisable for the manufacturer to perform an additional comparative multiple-dose study, to ensure that pharmacokinetic profiles are also similar at steady state, before starting the confirmatory clinical trial(s). In steady-state pharmacokinetic studies, the administration scheme should preferably use the highest dosage customarily recommended for the RBP.

The choice of single-dose studies, steady-state studies or repeated determination of pharmacokinetic parameters, and of the study population should be justified by the manufacturer. The cross-over design eliminates inter-subject variability and therefore, compared with the parallel design, reduces the sample size necessary to show equivalent pharmacokinetic profiles of the SBP and RBP. The treatment phases should be separated by an adequate wash-out phase to avoid carry-over effects. The cross-over design may not be appropriate for biological medicinal products with a long half-life or for proteins that are likely to provoke the formation of anti-product antibodies. In parallel designs, care should be taken to avoid relevant imbalances in all prognostic variables between treatment groups that may affect the pharmacokinetics of the drug substance (e.g. ethnic origin, smoking status, and extensive / poor metabolizer status of the study population).

Pharmacokinetic comparison of the SBP and the RBP should include not only absorption/bioavailability but also elimination characteristics, i.e. clearance and/or elimination half-life, which may differ between the SBP and the RBP.

Acceptance criteria for the demonstration of pharmacokinetic similarity between the SBP and the RBP should be predefined and appropriately justified. It should be noted that the criteria used in standard clinical pharmacokinetic comparability studies (bioequivalence studies) were developed for chemically derived, orally administered products and may not necessarily be applicable for biotherapeutic products. The lack of established acceptance criteria designed for biologicals means that the traditional 80–125% equivalence range is often used. However, if the 90% confidence intervals of the ratio of the population geometric means (test/reference) for the main parameters under consideration (usually rate and extent of absorption) fall outside this traditional range, the SBP may still be considered similar to the RBP provided that there is sufficient evidence of similarity from the quality, nonclinical, pharmacodynamic, efficacy and safety comparisons.

Other pharmacokinetic studies, such as interaction studies (with drugs likely to be used concomitantly) or studies in special populations (e.g. children, the elderly and patients with renal or hepatic insufficiency), are not usually required for an SBP.

Historically, limitations in the assay methodology for pharmacokinetic evaluation of peptide or protein products have restricted the usefulness of such studies. There should consequently be special emphasis on the analytical method selected and its ability to detect and follow the time course of the protein (the parent molecule and/or degradation products) in a complex biological matrix that contains many other proteins. The method should be optimized to provide satisfactory specificity, sensitivity and a range of quantification with adequate accuracy and precision.

In some cases, the presence of measurable concentrations of endogenous protein may substantially affect the measurement of the concentration–time profile of the administered exogenous protein. In such cases, the manufacturer should describe and justify the approach to minimize the influence of the endogenous protein on the results.

11.2. PHARMACODYNAMIC STUDIES

Although comparative clinical trials are usually required to demonstrate the similar efficacy and safety of the SBP and RBP, it may be advisable for the manufacturer to ensure similar pharmacodynamic profiles before proceeding to clinical trials, particularly if a difference in pharmacokinetic profiles, of unknown clinical relevance has been detected.

In many cases, pharmacodynamic parameters are investigated in the context of combined pharmacokinetic/pharmacodynamic studies. Such studies may provide useful information on the relationship between dose/exposure and effect, particularly if performed at different dose levels. In the comparative pharmacodynamic studies, pharmacodynamic effects should be investigated in a suitable population using a dose or doses within the steep part of the dose–response curve in order to maximize the chance of detecting potential differences between the SBP and the RBP. Pharmacodynamic markers should be selected on the basis of their clinical relevance.

11.3. CONFIRMATORY PHARMACOKINETIC/PHARMACODYNAMIC STUDIES

Clinical trials are usually required to demonstrate similar efficacy between the SBP and the RBP. In certain cases, however, comparative pharmacokinetic/pharmacodynamic studies may be appropriate, provided that:

- the pharmacokinetic and pharmacodynamic properties of the RBP are well characterized;
- at least one pharmacodynamic marker is a marker linked to efficacy (e.g. an accepted surrogate marker for efficacy); and
- the relationship between dose/exposure, the relevant pharmacodynamic marker(s) and response/efficacy of the RBP is established.

Euglycaemic clamp studies would be an example for acceptable confirmatory pharmacokinetic/pharmacodynamic studies for comparing the efficacy of two insulins. In addition, absolute neutrophil count and CD34+ cell count are the relevant pharmacodynamic markers for the activity of granulocyte colony stimulating factor (G-CSF) and could be used in pharmacokinetic/ pharmacodynamic studies in healthy volunteers to demonstrate the similar efficacy of two G-CSF-containing medicinal products.

The study population and dosage should represent a test system that is known to be sensitive to detect the potential differences between the SBP and the RBP. In the case of insulin, for

example, the study population should consist of non-obese healthy volunteers or patients with type 1 diabetes rather than insulin-resistant obese patients with type 2 diabetes. Otherwise, it will be necessary to investigate a relevant dose range to demonstrate that the test system is discriminatory. In addition, the acceptance ranges for demonstration of similarity in confirmatory pharmacokinetic and pharmacodynamic parameters should be predefined and appropriately justified. If appropriately designed and performed; such pharmacokinetic/pharmacodynamic studies are often more sensitive in detecting potential differences in efficacy than trials using clinical end-points.

11.4. EFFICACY STUDIES

Dose-finding studies are not required for an SBP. Demonstration of comparable potency, pharmacokinetic and pharmacodynamic profiles provide the basis for use of the RBP posology in the confirmatory clinical trial(s).

Similar efficacy of the SBP and the chosen RBP will usually have to be demonstrated in adequately powered, randomized and controlled clinical trial(s). The principles of such trials are laid down in relevant ICH guidelines. Clinical studies should preferably be double-blind or at a minimum observer blind. In the absence of any blinding, careful justification will be required to prove that the trial results are free from significant bias.

Potential differences between the SBP and the RBP should be investigated in a sensitive and preferably well-established clinical model. In the case of growth hormone (GH), for example, treatment-naive children with GH deficiency usually represent the most appropriate study population, as opposed to children with non- GH-deficient short stature who are usually less sensitive to the effects of GH. Although adult patients with GH deficiency could also be considered a “sensitive” population, the end-point used to measure the effects of GH treatment (i.e. body composition) is less sensitive than the one used in children (i.e. longitudinal growth), making an equivalence or non-inferiority margin more difficult to define.

In principle, equivalence designs (requiring lower and upper comparability margins) are clearly preferred for comparing the efficacy and safety of the SBP and the RBP. Non-inferiority designs (requiring only one margin) may be considered if appropriately justified. While both designs can be used, their advantages and disadvantages should be well understood. The designs should be chosen with due regard to the possible advantages and disadvantages of each (see “Advantages

and disadvantages of equivalence/non-inferiority designs for SBPs" below). For statistical considerations see section "Statistical considerations for the design and analysis of equivalence/non-inferiority trials for SBPs" below.

Equivalence/non-inferiority margins must be pre-specified and justified on the basis of clinical relevance; that is, the selected margin should represent the largest difference in efficacy that would not matter in clinical practice. Treatment differences within this margin would be thus, by definition acceptable because they have no clinical relevance.

Similar efficacy implies that similar treatment effects can be achieved when using the same dosage(s); in the head-to-head comparative trial(s), the same dosage(s) of SBP and RBP should be used. In cases where the medicinal product is titrated according to treatment response (e.g. epoetin or insulin) rather than being given at a fixed dosage (e.g. somatropin in GH-deficient children), equivalence/non-inferiority should be demonstrated with regard not only to treatment response but also to dosage. This is best achieved by defining co-primary end-points that also include dosage.

Generally, equivalence trials are clearly preferable to ensure that the SBP is not clinically less or more effective than the RBP when used at the same dosage(s). For medicinal products with a wide safety margin, non-inferiority trials may also be acceptable. However, it should be considered that non-inferior efficacy, by definition, does not exclude the possibility of superior efficacy of the SBP compared with the RBP; this, if clinically relevant, would contradict the principle of similarity.

Before starting the confirmatory clinical trial, all comparative data generated up to this point should therefore be carefully reviewed and analysed to ascertain similarity of the SBP and the RBP. The confirmatory trial marks the last step of the comparability exercise and prior demonstration of similar physicochemical characteristics, potency and pharmacokinetic/ pharmacodynamic profiles make superior efficacy of the SBP compared with the RBP highly unlikely. However, in the rare event that, after completion of the study, the results indeed indicate statistically superior efficacy, any clinical relevance of this superiority should be excluded: it could be associated with increased adverse events if the SBP is prescribed at the same dosage as the RBP. In the case of an equivalence trial, clinically meaningful differences – including superior efficacy – between the SBP and the RBP are excluded if the 95% confidence

interval of the treatment difference is fully contained within the pre-specified two-sided (upper and lower) comparability margins. In the case of a non-inferiority trial, a post-hoc justification of superior efficacy, if observed, having no clinical relevance may be more difficult.

Whatever the predefined study design; the real results obtained from the clinical trial(s) will determine whether the SBP and the RBP can be considered to be clinically similar. If clinically relevant differences are found, the new product should not be considered to be similar to the RBP and should be developed as a stand-alone product.

Whereas several examples exist for licensing of SBPs based on equivalence trials (e.g. recombinant human GH, epoetin and G-CSF in the European Union), experience with non-inferiority trials for this purpose is limited and based principally on theoretical considerations. An additional advantage of demonstrating equivalent efficacy (rather than non-inferior efficacy) is that this would provide a stronger rationale for the possibility of extrapolation of efficacy data to other indications of the RBP, particularly if these include different dosages from that (or those) tested in the clinical trial (see section 11.7).

11.4.1. Advantages and disadvantages of equivalence/ non-inferiority designs for SBPs

An equivalence trial is designed to confirm the absence of a clinically meaningful difference between the SBP and the RBP. This is the most suitable design for confirming that the SBP is equivalent to the RBP; this is in line with the principle of similarity, since a non-inferiority trial does not exclude the possibility that the SBP is shown to be statistically and clinically superior to the RBP (which contradicts the principle of similarity). Table 1 below highlights the advantages and disadvantages of each design.

11.4.2. Statistical considerations for the design and analysis of equivalence/non-inferiority trials for SBPs

As indicated above, equivalence or non-inferiority studies may be acceptable for the comparison of efficacy and safety of the SBP and the RBP. The choice of clinical trial design will depend on the product in question, its intended use, disease prevalence and the target population. The specific design selected for a particular study should be clearly stated in the trial protocol and justified. Complex and often very subtle, statistical issues are involved in the design, analysis and interpretation of equivalence and non-inferiority trials. This section is intended to emphasize

the importance of the points that need to be considered in designing and analysing equivalence and non-inferiority trials; it does not provide a comprehensive overview of all statistical considerations. In particular, a good understanding of statistical confidence intervals and their application to equivalence and non-inferiority clinical trials is essential.

Irrespective of the trial design selected, a comparability margin should be specified during trial design and clearly documented in the study protocol. For an equivalence trial, both the lower and upper equivalence margins are required, while only one margin is required for a non-inferiority trial. The selection of the margin should be given careful consideration and should be justified both statistically and clinically. Adequate evidence of the effect size of the RBP should be provided to support the proposed margin. The magnitude and variability of the effect size of the RBP derived from historical trials should also be taken into consideration in determining the comparability margin in terms both of the end-point chosen and of the population to be studied. There must be reasonable assurance that the study is capable of showing any difference that exists between the RBP and SBP; this is referred to as "assay sensitivity".

Table 1: Advantages and disadvantages of equivalence/non-inferiority designs for SBPs

Design	Advantage	Disadvantage
Equivalence	Demonstration of equivalence provides a strong rationale for the possibility of extrapolation of efficacy to other indications of the RBP. Current experience for the licensing of SBPs is based on equivalence trials.	An equivalence trial tends to need a larger sample size to achieve the same study power as a non-inferiority trial. A finding of superiority would lead to the failure of the equivalence trial. There would be no option to show that the superiority observed is not clinically relevant. However, a stand-alone application might still be an option, subject to a requirement for additional studies
Non-Inferiority	A non-inferiority trial requires a smaller sample size to achieve the same study power	Post-hoc justification that a finding of statistically superior efficacy is not clinically relevant is difficult. If the superiority observed is considered

	as an equivalence trial. A finding of superiority of the SBP compared to the RBP would not lead to failure of a non-inferiority trial, provided that it can be demonstrated that the superiority observed is not clinically relevant.	clinically relevant, the SBP would not be considered to be similar to the RBP and should be developed as a stand-alone product. Demonstration that superior efficacy of the SBP, prescribed at the same dosage as the RBP, is not associated with increased adverse events would be required in all cases. Demonstration of non-inferiority does not provide a strong rationale for the possibility of extrapolation to other indications of the RBP. There is currently no experience with licensing of SBPs based on non-inferiority trials.

Statistical analysis for both equivalence and non-inferiority designs is generally based on the use of two-sided confidence intervals (typically at the 95% level) for the difference between treatments. For equivalence trials, equivalence is demonstrated when the entire confidence interval falls within the lower and upper equivalence margins. Non-inferiority evaluations are one sided and statistical inference is based only on the lower or upper confidence limit whichever is appropriate for a given study. For example, if a lower margin is defined, non-inferiority is demonstrated when the lower limit of the confidence interval is above the non-inferiority margin. Analysis of non-inferiority trials can also be based on a one-sided confidence interval at the 97.5% level.

Details of the sample size calculations should be provided in the study protocol. The basis of estimates of any quantities used in the sample size calculation should also be clearly explained, and these estimates will usually be based on results from earlier trials with the RBP or on published literature. Since the formulae for sample size calculations are slightly different between equivalence and non-inferiority trials, and the two-sided equivalence trial tends to need a larger sample size than a one-sided non-inferiority trial, sample size calculations should be based on methods specifically designed for equivalence or non-inferiority trials. In estimating the sample size for equivalence or non-inferiority trials, it is usually assumed that there is no difference between the SBP and the RBP. An equivalence trial could be underpowered if the

true difference is not zero. Similarly, a non-inferiority trial could be underpowered if the SBP is actually less effective than the RBP. Determination of the appropriate sample size is dependent on various factors including: the type of primary end-point (e.g binary, quantitative or time-to-event), the predefined comparability margin, the probability of a type I error (falsely rejecting the null hypothesis) and the probability of a type II error (erroneously failing to reject the null hypothesis). Keeping the probability of a type II error low will increase the ability of the study to show equivalence or non-inferiority of the SBP to the RBP. The expected rates of patient dropouts and withdrawals should also be taken into consideration in the determination of the sample size.

11.5. SAFETY

Pre-licensing safety data should be obtained in a sufficient number of patients to characterize the safety profile of the SBP. Depending on their size and duration, efficacy trials may be sufficient or may need to be extended to provide an adequate safety database. Comparison with the RBP should include type, frequency and severity of adverse events/reactions. For cases in which similar efficacy is demonstrated in confirmatory pharmacokinetic/pharmacodynamic studies but safety data relevant for the target population cannot be deduced from these studies, data on safety in the target population are still needed. For example, for two soluble insulins, the euglycaemic clamp study is considered the most sensitive method for detecting differences in efficacy. However, immunogenicity and local tolerance of subcutaneously administered SBP cannot be assessed in such a study and should therefore be evaluated in the target population. Safety data should preferably be comparative. Comparison with an external control group is usually hampered by differences in the investigated patient population and concomitant therapy, observation period and/or reporting.

Safety data obtained from the clinical trials can be expected mainly to detect frequent and short-term adverse events/reactions. Such data are usually sufficient pre-licensing, but further close monitoring of clinical safety of the SBP is usually necessary in the post-marketing phase (see section 12).

11.6. IMMUNOGENICITY

Immunogenicity of biotherapeutic products should always be investigated preauthorization. Even if efficacy and safety of an SBP and RBP have been shown to be similar, immunogenicity may still be different.

The immune response to a biotherapeutic is influenced by many factors including the nature of the drug substance, product- and process-related impurities, excipients and stability of the product, route of administration, dosing regimen, and patient-, disease- and/or therapy-related factors.

The consequences of unwanted immunogenicity may vary considerably, from the clinically irrelevant to the serious and life-threatening. Although neutralizing antibodies directly alter the pharmacodynamic effect of a product (i.e. by directly blocking an active site of the protein), binding antibodies often affect pharmacokinetics and thereby also influence pharmacodynamics. Thus, an altered effect of the product as a consequence of anti-product antibody formation might be a composite of pharmacokinetic, pharmacodynamic and safety effects.

Immunogenicity of a biotherapeutic should always be investigated in humans since animal data are usually not predictive of the immune response in humans. The frequency and type of antibodies induced, as well as the possible clinical consequences of the immune response, should be compared for the SBP and the RBP. Comparison with an external control group is not considered appropriate because it is usually hampered by differences in the investigated patient population, observation period, sampling time points, assays employed, and interpretation of results.

Generally, the amount of immunogenicity data obtained from the comparative efficacy trial(s) (i.e. trials that are powered for their primary efficacy end-point) will allow detection of a marked increase in immunogenicity of the SBP compared with the RBP and will be sufficient pre-licensing. Where clinically meaningful or even serious antibody development has been encountered with the RBP (or the substance class) but is too rare to be captured pre-licensing (e.g. cross-reacting neutralizing anti-epoetin antibodies causing pure red cell aplasia), a specific risk management plan for the SBP may be necessary to assess this specific risk post-marketing (see section 12). In case similar efficacy is demonstrated in confirmatory pharmacokinetic/pharmacodynamic studies, immunogenicity data in the target population are

still needed (see section 11.5). If the manufacturer intends to extrapolate efficacy and safety data to other approved indications of the RBP (see section 11.7), care should be taken to ensure that immunogenicity is investigated in the patient population that carries the highest risk of an immune response and immune-related adverse events.

The manufacturer will need to justify its antibody testing strategy including the selection, assessment and characterization of assays, identification of appropriate sampling time points including baseline, sample volumes and sample processing/storage as well as selection of statistical methods for analysis of data. Antibody assays need to be validated for their intended purpose. A screening assay of sufficient sensitivity should be used for antibody detection and a neutralization assay should be available for further characterization of antibodies, if present. Possible interference of the circulating antigen with the antibody assay(s) should be taken into account. Detected antibodies need to be further characterized and their potential clinical implications for safety, efficacy and pharmacokinetics evaluated. For example, the isotype of the antibodies should be determined if they may be predictive of safety (e.g. development of IgE antibodies correlates with the development of allergic and anaphylactic responses). If the antibody incidence is higher with the use of the SBP compared to the RBP, the reason for the difference needs to be investigated. Special attention should be paid to the possibility that the immune response seriously affects the endogenous protein and its unique biological function.

The required observation period for immunogenicity testing will depend on the intended duration of therapy and the expected time of antibody development and should be justified by the manufacturer. In the case of chronic administration, one-year data will usually be appropriate pre-licensing to assess antibody incidence and possible clinical implications. This is the case, for example, for somatropin-containing products, where antibody development usually occurs within the first 6–9 months of treatment but potential effects on growth are only seen thereafter. In some cases, shorter pre-licensing observation periods may be sufficient; for insulins, for example, most susceptible patients will develop antibodies within the first 6 months of treatment and clinical consequences, if any, would usually be observed at about the same time as antibody development. If considered clinically relevant, development of antibody titres, their persistence over time, potential changes in the character of the antibody response and the possible clinical implications should be assessed pre- and post-marketing.

Since pre-licensing immunogenicity data are often limited, further characterization of the immunogenicity profile may be necessary during post-marketing, particularly if rare antibody-related serious adverse events may occur that are not likely to be detected in the pre-marketing phase.

11.7. EXTRAPOLATION OF EFFICACY AND SAFETY DATA TO OTHER CLINICAL INDICATIONS

If similar efficacy and safety of the SBP and RBP have been demonstrated for a particular clinical indication, extrapolation of these data to other indications of the RBP (not studied in independent clinical studies with the SBP) may be possible if all of the following conditions are fulfilled:

- A sensitive clinical test model has been used that is able to detect potential differences between the SBP and the RBP.
- The clinically relevant mechanism of action and/or involved receptor(s) are the same; e.g. GH action in different conditions of short stature in children; erythropoiesis-stimulating action of epoetins in different conditions associated with anaemia or for the purpose of autologous blood donation. If the mechanism of action is different or not known, a strong scientific rationale and additional data (e.g. "pharmacodynamic fingerprint", additional clinical data) will be needed.
- Safety and immunogenicity of the SBP have been sufficiently characterized and no unique or additional safety issues are expected for the extrapolated indication(s), for which clinical data on the SBP are not being provided; e.g. immunogenicity data in immunosuppressed patients would not allow extrapolation to an indication in healthy subjects or patients with autoimmune diseases, although the reverse would be valid.
- If the efficacy trial used a non-inferiority study design and demonstrated acceptable safety and efficacy of the SBP compared to the RBP, the applicant should provide convincing arguments that this finding can be applied to the extrapolated indications; e.g. results from a non-inferiority trial in an indication where a low dose is used may be difficult to extrapolate to an indication where a higher dose is used, from the standpoint of both efficacy and safety.

If these prerequisites for extrapolation of efficacy and safety data of the SBP to other indication(s) of the RBP are not fulfilled, the manufacturer will need to submit own clinical data to support the desired indication(s). If extrapolation of results from clinical studies for one indication to one or more different indications is intended, a detailed scientific discussion on the risk–benefit of such a proposal should be provided, based on the above criteria.

12. PHARMACOVIGILANCE

As for most biological medicines, data from pre-authorization clinical studies are usually too limited to identify all potential unwanted effects of an SBP. In particular, rare adverse events are unlikely to be encountered in the limited clinical trial populations being tested with the SBP. Further close monitoring of the clinical safety of an SBP in all approved indications and a continued benefit– risk assessment are therefore necessary in the post-marketing phase.

The manufacturer should submit a safety specification and pharmacovigilance plan at the time of submission of the marketing authorization application. The principles of pharmacovigilance planning can be found in relevant guidelines such as ICH E2E. The safety specification should describe important identified or potential safety issues for the RBP and for the substance class and/or any that are specific for the SBP. The pharmacovigilance plan should describe the planned post-marketing activities and methods based on the safety specification. In some cases, risk minimization measures such as educational material for patients and/or treating physicians may enhance the safe use of the SBP.

Any specific safety monitoring imposed on the RBP or product class should be incorporated into the pharmacovigilance plan for the SBP, unless a compelling justification can be provided to show that this is not necessary. Moreover, potential additional risks identified during the review of the data obtained with the SBP should be subject to further safety monitoring (e.g. increased immunogenicity that might result from a difference in the glycosylation profile).

Post-marketing safety reports should include all information on product tolerability received by the marketing authorization holder. The safety information must be evaluated in a scientific manner and should include evaluation of the frequency and causality of adverse events.

Manufacturers should ensure that, at the time of the marketing authorization, they have in place an appropriate pharmacovigilance system, including the services of a qualified person

responsible for monitoring pharmacovigilance and the necessary means for notification of adverse reactions that occur in any of the countries where the product is marketed.

After the marketing authorization is granted, it is the responsibility of the authority to monitor closely the compliance of manufacturers with their marketing commitments, where appropriate, and particularly with their pharmacovigilance obligations (as previously described).

In addition, as for all biotherapeutics, an adequate system for ensuring specific identification of the SBPs (i.e. traceability) is essential. The applicant need to follow the Guideline for Adverse Event Monitoring (Pharmacovigilance) of the Authority, current Edition, for safety monitoring and ensure the ability to identify any biotherapeutic marketed in Ethiopia that is the subject of adverse reaction reports. The adverse reaction report for any biotherapeutic should include, in addition to the International Nonproprietary Name (INN), other important indicators such as proprietary (brand) name, manufacturer's name, lot number and country of origin.

13. PRESCRIBING INFORMATION AND LABEL

The SBP should be clearly identifiable by a unique brand name. Where an INN is defined, this should also be stated; WHO policy on INN should be followed. Provision of the lot number is essential; it is an important part of production information and critical for traceability whenever problems with a product are encountered.

The prescribing information for the SBP should be as similar as possible to that of the RBP except for product-specific aspects, such as different excipient(s). This is particularly important for posology and safety-related information, including contraindications, warnings and adverse events. However, if there are fewer indications for the SBP than for the RBP, the related text in various sections may be omitted unless it is considered important to inform doctors and patients about certain risks, e.g. as a result of potential off-label use. In such cases it should be clearly stated in the prescribing information that the SBP is not intended for use in the specific indication(s) and the reasons why. The Authority may choose to mention in the product information the SBP nature of the product, the studies that have been performed with the SBP and the specific RBP, and/or to include instructions for the prescribing physician on how to use SBP products.

ANNEXES

ANNEX I: APPLICATION FORM FOR REGISTRATION

Food, Medicine and Healthcare Administration and Control Authority of Ethiopia

P.O.Box 5681, Addis Ababa, Ethiopia

A. Type of application (check the box applicable)

New Application	□
Re-registration	□
Variation to existing marketing authorization (If selected, complete the information below.)	□
• Previous registration number	
• Previous registration condition	
• Brief description of change intended	
• Reasons for variations	

B. Details on the product

Proprietary name (trade name)	
Approved generic name (s) (use INN if any)	
Standard claimed (BP, Ph.In, Ph. Eur., USP, IH, etc.)	
Strength(s) per dosage unit	
Dosage form	
Route of administration	
Shelf life (months)	
Storage condition	

Visual description			
Description of container closure			
Packaging and pack size			
Therapeutic category			
Use category	Scheduled Narcotic □		
	Prescription only □		
	Hospital use only □		
	Pharmacy □		
	Over-the-counter (OTC) □		
Complete qualitative and quantitative composition (indicate per unit dosage form, e.g., per 5ml, etc.)** ** Add/delete as many rows and columns as needed.	Composition	Strength	Function
Complete qualitative and quantitative composition (indicate per batch in Kg, L, etc.)	Composition	Strength	Function

Statement of similarity and difference of clinical, bio-batch, stability, validation, and commercial batch sizes			
Regulatory situation in other country (Provide a list of countries in which this product has been granted a marketing authorization and the restrictions on sale or distribution, e.g., withdrawn from the market, etc.)			

C. Details on the applicant

Name	
Business address	
Street number and postal address	
Telephone number	
Fax number	
E-mail and website address	
Contact person in a company	Name:
	Position:
	Postal address:
	Telephone number:
	Fax number:
	E-mail:
Details of Manufacturer, if different from above	<<Insert the required information as indicated above>>>

D. Details on active pharmaceutical(s) ingredient(s)

Name of manufacturer	
Street and postal address	
Telephone	
Fax number	
E-mail	
Name of the active ingredient	
Retest period/Shelf life	

E. Details on local agent (representative) in Ethiopia

Name of local agent	
Sub-city and postal address	
Telephone	
Fax number	
E-mail	
Contact person in company	

F. Details on dossiers submitted with the application

Section of dossier	**Annex, page number, etc.**
Administrative and product information	
Quality	
Non Clinical Evaluation	
Clinical Evaluation	

CERTIFICATION BY A RESPONSIBLE PERSON IN THE APPLICANT COMPANY

I, the undersigned, certify that all the information in the accompanying documentation concerning an application for a marketing authorization for:

Proprietary name (trade name)	
Approved generic name(s) (INN)	
Strength(s) per dosage unit	
Dosage form	
Applicant	
Manufacturer	

… is correct and true, and reflects the total information available. I further certify that I have examined the following statements and I attest to their accuracy.

1. The current edition of the WHO Guideline, "Good manufacturing practices for Biological products," is applied in full in all premises involved in the manufacture of this product.
2. The formulation per dosage form correlates with the master formula and with the batch manufacturing record forms.
3. The manufacturing procedure is exactly as specified in the master formula and batch manufacturing record forms.
4. Each batch of all starting materials is either tested or certified against the full specifications in the accompanying documentation and comply fully with those specifications before it is released for manufacturing purposes.
5. All batches of active pharmaceutical ingredient(s) are obtained from the source(s) specified in the accompanying documentation.
6. No batch of active pharmaceutical ingredient will be used unless a copy of the batch certificate established by the active ingredient manufacturer is available.

7. Each batch of the container/closure system is tested or certified against the full specifications in the accompanying documentation and complies fully with those specifications before it is released for manufacturing purposes.
8. Each batch of the finished product is either tested or certified against the full specifications in the accompanying documentation and complies fully with the release specifications before it is released for sale.
9. The person releasing the product for sale is an authorized person as defined by the WHO guideline "Good manufacturing practices: Authorized person - the role, functions and training."
10. The procedures for control of the finished product have been validated for this formulation.
11. The market authorization holder has a standard operating procedure for handling adverse reaction reports on its products.
12. The market authorization holder has a standard operating procedure for handling batch recalls of its products.
13. All the documentation referred to in this Certificate is available for review during a GMP inspection.
14. Any clinical trials were conducted according to WHO's "Guidelines for good clinical practice (GCP) for trials on pharmaceutical products."

Signature_____

Name _____

Position in company (print or type) _____

Date: _____

ANNEX II: CERTIFICATE OF PHARMACEUTICAL PRODUCTS[1]

This certificate conforms to the format recommended by the World Health Organization

(General instructions and explanatory notes attached)

Certificate No. _____

Exporting (certifying country): _____

Importing (requesting country): _____

1. Name and dosage form of the product: _____

1.1. Active ingredient(s)[2] and amount(s) per unit dose[3]: _____

For complete composition including excipients, see attached[4]: _____

1.2. Is this product licensed to be placed on the market for use in the exporting country?[5]

yes/no (*Key in as appropriate*)

1.3 Is this product actually on the market in the exporting country? (*Key in as appropriate*)

yes/no/unknown

If the answer to 1.2. is **yes**, continue with section 2A and omit section 2B. If the answer to 1.2 is no, omit section 2A and continue with section 2B:[6]

2.A.1. Number of product license[7] and date of issue:

_____

2.A.2. Product license holder (name and address):

_____

2.A.3. Status of product license holder:[8]

a/b/c *(Key in appropriate category as defined in note 8)*

2.A.3.1. For categories (b) and (c), provide the name and address of the manufacturer producing the dosage form:[9] _____

2.A.4. Is a summary basis for approval appended?[10]

yes/no (*Key in as appropriate*)

2.A.5. Is the attached, officially approved product information complete and consonant with the license?[11]

yes/no/not provided (*Key in as appropriate*)

2.A.6. Applicant for Certificate, if different from license holder (name and address):[12]

_____--

2.B.1. Applicant for Certificate (name and address):

_____

2.B.2. Status of applicant:

a b/c (*Key in appropriate category as defined in footnote 8)*

2.B.2.1. For categories (b) and (c), provide the name and address of the manufacturer producing the dosage form:[9] _____

2.B.3. Why is marketing authorization lacking?

not required/not requested/under consideration/refused (*Key in as appropriate*)

2.B.4. Remarks:[13]

3. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced?

If not or not applicable, proceed to question 4.

yes/no/not applicable[14] (*Key in as appropriate*)

3.1. Periodicity of routine inspections (years): _____

3.2. Has the manufacture of this type of dosage form been inspected?

yes/no

3.3. Do the facilities and operations conform to good manufacturing practices (GMP) as recommended by the World Health Organization (WHO)?[15]

yes/no/not applicable[14] (*Key in as appropriate*)

4. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product:[16]

yes/no *(Key in as appropriate)*

If no, explain: _____

Address of certifying authority: _____

Telephone: _____

Fax No:_____

E-mail: _____

Name of authorized person: _____

Signature: _____

Stamp and date: _____

General instructions

Please refer to the Guideline for full instructions on how to complete this form and for information on the implementation of the Scheme.

This form should always be submitted as a hard copy, with responses printed in type rather than handwritten.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes

[1] This Certificate, which is in the format recommended by WHO, establishes the status of the pharmaceutical product and of the applicant for the Certificate in the exporting country. It is for a single product only, since manufacturing arrangements and approved information for different dosage forms and different strengths can vary.

[2] Use, whenever possible, the International Nonproprietary Names (INNs) or national nonproprietary names.

[3] The formula (complete composition) of the dosage form should be given on the Certificate or should be appended.

[4] Details of quantitative composition are preferred, but their provision is subject to the agreement of the product-license holder.

[5] When applicable, append details of any restriction applied to the sale, distribution, or administration of the product that is specified in the product license.

[6] Sections 2A and 2B are mutually exclusive.

[7] Indicate, when applicable, if the license is provisional, or the product has not yet been approved.

[8] Specify whether the person responsible for placing the product on the market:

(a) manufactures the dosage form;

(b) packages and/or labels a dosage form manufactured by an independent company; or,

(c) is not involved in any of the above.

[9] This information can only be provided with the consent of the product-license holder or, in the case of non-registered products, the applicant. Non-completion of this section indicates that the party concerned has not agreed to inclusion of this information.

It should be noted that information concerning the site of production is part of the product license. If the production site is changed, the license has to be updated or it is no longer valid.

[10] This refers to the document, prepared by some national regulatory authorities, that summarizes the technical basis on which the product has been licensed.

[11] This refers to product information approved by the competent national regulatory authority, such as Summary Product Characteristics (SPC).

[12] In this circumstance, permission for issuing the Certificate is required from the product-license holder. This permission has to be provided to the Authority by the applicant.

[13] Please indicate the reason that the applicant has provided for not requesting registration.

(a) the product has been developed exclusively for the treatment of conditions — particularly tropical diseases — not endemic in the country of export;

(b) the product has been reformulated with a view to improving its stability under tropical conditions;

(c) the product has been reformulated to exclude excipients not approved for use in pharmaceutical products in the country of import;

(d) the product has been reformulated to meet a different maximum dosage limit for an active ingredient; or,

(e) any other reason (please specify).

[14] Not applicable means the manufacture is taking place in a country other than that issuing the product Certificate and inspection is conducted under the aegis of the country of manufacture.

[15] The requirements for good practices in the manufacture and quality control of drugs referred to in the Certificate are those included in the Thirty-second Report of the Expert Committee on Specifications for Pharmaceutical Preparations, WHO Technical Report Series No. 823, 1992, Annex 1. Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (WHO Technical Report Series, No. 822, 1992, Annex 1).

[16] This section is to be completed when the product-license holder or applicant conforms to status (b) or (c), as described in note 8 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances, the applicant should supply the certifying authority with information to identify the contracting parties responsible for each stage of manufacture of the finished dosage form, and the extent and nature of any controls exercised over each of these parties.

ANNEX III: SUMMARY OF PRODUCT CHARACTERISTICS

(With proposed sentence patterns and illustrative examples)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

   {(Invented) name of product <strength><pharmaceutical form>}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

   For excipients, see 6.1.

3. PHARMACEUTICAL FORM

4. CLINICAL PARTICULARS

   4.1. Therapeutic indications

   <This pharmaceutical product is for diagnostic use only. >

   4.2. Posology and method of administration [*See example below*.]

   Adults

   Children and adolescents (4 to 17 years of age)

   General administration recommendations

   Special dosing considerations in adults

   4.3. Contraindications

   <Hypersensitivity to the API(s) or to any of the excipients <or {residues}>

   4.4. Special warnings and special precautions for use [*See example below*.]

   Drug interactions

   Acute hemolytic

   Hyperglycemia

   Patients with coexisting conditions

   4.5. Interaction with other FPPs and other forms of interaction [*See example below*.]

   Rifabutin)

   Ketoconazole)

   Itraconazole)

   Nevirapine)

   HMG -CoA reductase inhibitors)

   Rifampicin)

4.6. Pregnancy and lactation [*See example below*.]

Use during pregnancy)

Use during lactation)

4.7. Effects on ability to drive and use machines

< {Invented name} has <no or negligible influence><minor or moderate influence><major influence> on the ability to drive and use machines.> [describe effects where applicable]

<No studies on the effects on the ability to drive and use machines have been performed.><Not relevant.>

4.8. Undesirable effects [*See example below*.]

Laboratory test findings)

Post-marketing experience)

4.9. Overdose

<No case of overdose has been reported.>

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: {group}

ATC code: {code}

Mechanism of action

Microbiology (when applicable)

Drug resistance (when applicable)

Cross resistance (when applicable)

Pharmacodynamic effects

Adults

Pediatric patients

5.2. Pharmacokinetic properties

Absorption

Distribution

Biotransformation

Elimination

Characteristics in patients

5.3. Preclinical safety data

<Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.><Preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.>

<Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows.>

Mutagenicity

Carcinogenicity

Developmental Toxicity

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients [*See example below*.]

Capsule content)

Capsule shell)

Printing ink)

6.2. Incompatibilities

<Not applicable.>

<In the absence of compatibility studies, this pharmaceutical product must not be mixed with other pharmaceutical products.>

<This pharmaceutical product must not be mixed with other pharmaceutical products except those mentioned in 6.6.>

6.3. Shelf life

<...><6 months><...><1 year><18 months><2 years><30 months><3 years><...>

6.4. Special precautions for storage

<Do not store above <25°C> 30°C»

<Store at 2°C - 8°C (in a refrigerator» <Store in a freezer>

<Do not <refrigerate><or><freeze»

<Store in the original <package><container» <Keep the container tightly closed>

<Keep the container in the outer carton>

<No special precautions for storage>

<in order to protect from <light><moisture»

6.5. Nature and contents of container

<Not all pack sizes may be marketed.>

6.6. Instructions for use and handling <and disposal>

<No special requirements.>

7. MARKETING AUTHORISATION HOLDER
8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION OF EXPORTING COUNTRY
10. DATE OF REVISION OF THE TEXT

ANNEX IV: REQUIREMENTS FOR REGISTRATION OF PRODUCTS ACCEPTED BY STRINGENT REGULATORY AUTHORITY

General Principle

Stringent Regulatory Authorities are national medicine regulatory authorities and international organization recognized and listed as a stringent by the EFMHACA. When the product application has been submitted and accepted in countries such as United States of America, Canada, Australia, Norway, Finland, France Denmark, Netherlands, Austria, Japan, EMA, Switzerland, Belgium, Germany, Italy, Ireland, UK, and WHO Prequalification Programme are considered to be products registered with a Stringent Regulatory Authority (SRA).

The purpose of this guidance is neither to eliminate the requirement of dossier submission nor to limit the Authority for full assessment of the product, whenever deemed to be necessary, the main purpose is to introduce a procedure that will facilitate the registration of innovator products as well as products accepted through the WHO Prequalification Programme (PQP) in order to enhance the availability of the medicines to the public.

The rationale behind the introduction of these procedures is that:

1. Most of the requirements and principles stipulated in this Guideline are derived from the guidance developed by ICH regions and associated countries, and from WHO Guidelines;
2. Whenever necessary, full assessment of the dossiers of the innovators can be done at any time; and,
3. The clinical studies, as well as the acceptance of the medicines for the general public health benefit, have been accepted.

An applicant claiming to have a registration certificate issued by an SRA, as defined above, should submit complete dossiers. At the time of registration by the Authority, the information that needs to be assessed is:

1. Full information under Administrative and product information section of this Guideline
2. Public assessment report(s) and/or final acceptance letter issued by a national regulatory authority in an ICH region and associated countries (e.g., summary of product characteristics and Certificate of Pharmaceutical Product);

3. In the case of a WHO Prequalified product, the final acceptance letter and a copy of the WHO Public Assessment Report (WHOPAR);
4. A Quality Assurance-certified copy of the Marketing Authorization issued by the relevant SRA;
5. If the composition/formulation, strength, specifications, etc., are different from the prequalified product or the product for which the marketing authorization Certificate was issued recognized SRA, arguments and/or data to support the applicability of the Certificate(s), and demonstration of clinical equivalence;
6. If the primary packaging material of the product is different from that approved by the national regulatory authorities of the ICH regions and associated countries or WHO PQP, then all stability testing data;
7. Written commitment letter to notify the Authority that whenever a pending variation, notice of concern, withdrawal, or recall is initiated, the same shall be communicated to the Authority; and,
8. Evidence of a minimum of five (5) years of current and continuous manufacturing experience and a copy of the last Annual Product Report. Specific issues on manufacturing experience will be address on case-by-case basis by the Authority.